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Abstract

Myelin-specific encephalitogenic T cells, when passively transferred into rats or mice, cause an experimental autoimmune disease. Previous studies by our group have shown that (a) the same cells also significantly reduce post-traumatic degeneration in these animals after injury to the central nervous system, (b) this beneficial autoimmunity is a physiological response, and (c) animals differ in their ability to resist injurious conditions, and the ability to resist post-traumatic degeneration correlates with resistance to the development of an autoimmune disease. Here we show that optic nerve neurons in both resistant and susceptible rat strains can be protected from secondary degeneration after crush injury by immunization with myelin basic protein emulsified in complete or incomplete Freund's adjuvant. We provide evidence that potentially destructive autoimmunity (causing autoimmune disease) and beneficial autoimmunity (causing improved neuronal survival) both result from activity of the same myelin-specific, proinflammatory Th1 cells. We further show that following passive transfer of such Th1 cells, the expression of their beneficial potential depends on the activity of an additional T cell ($CD4^+$) population. By identifying the additional cellular component of autoimmune neuroprotection, we may be able to take meaningful steps toward achieving neuroprotection without risk of accompanying autoimmune disease.

Keywords: Myelin specific Th1 cell; Post-traumatic protective autoimmunity; Neuroprotection

1. Introduction

Autoimmunity has long been viewed as a destructive response to harmful self-components. However, our research group recently provided evidence that autoimmunity is the body's endogenous response to a central nervous system (CNS) injury, and that its purpose is beneficial (Schwartz and Kipnis, 2001; Yoles et al., 2001). This conclusion is based on experimental findings in rodents, demonstrating that (a) passive transfer of encephalitogenic (disease-inducing) T cells reactive to myelin basic protein (MBP) reduces post-injury neuronal losses relative to those of controls (Butovsky et al., 2001; Hauben et al., 2000a,b; Moalem et al., 1999, 2000b); (b) immune neuroprotection can also be exerted by transfer of autoimmune T cells that recognize non-encephalitogenic epitopes (Kipnis et al., 2000; Moalem et al., 1999); (c) the beneficial effect of these autoreactive T cells is not merely the result of an experimental manipulation, but is a physiological response to CNS insult (Schwartz and Kipnis, 2001; Yoles et al., 2001); and (d) the ability to spontaneously exhibit this endogenous autoimmune neuroprotection varies among individuals and is directly correlated to the individual's genetically determined resistance to the development of the transient monophasic autoimmune disease known as experimental autoimmune encephalomyelitis (EAE) (Kipnis et al., 2001; Lundberg et al., 2001; Schwartz and Kipnis, 2001).

In view of these findings, we were interested in determining the nature of the relationship between encephalitogenic and beneficial autoimmune T cells. We also wanted to find out whether the two functions (disease induction and neuroprotection) are served by the same cells, and if so, what makes them encephalitogenic in certain circumstances and beneficial in others (Cohen and Schwartz, 1999; Hafler and Weiner, 1987; Hohlfeld et al., 2000; Steinman, 2001; Wekerle, 1998).

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In this study, we show that induction of an autoimmune disease is not a necessary condition for autoimmune neuroprotection. Thus, for example, immunization of susceptible strains of rats or mice with MBP emulsified in incomplete Freund's adjuvant (IFA) was found to confer neuroprotection without causing disease development. We further show that the same T cell population participates both in the manifestation of autoimmune disease symptoms and in beneficial autoimmunity. However, the passive transfer of autoimmune T cells (Th1), in order to have a beneficial outcome, was found to require the participation of the injected Th1 cells directed to myelin antigens and of an additional $CD4^+$ T cell population of the recipient. Furthermore, the injected Th1 cells in order to display neuroprotection should be viable autoreactive T cells, as demonstrated by the failure of injection of lethally irradiated T cells to improve neuronal survival.

2. Materials and methods

2.1. Animals

Inbred adult female Lewis and Sprague–Dawley (SPD) rats, adult wild-type C57Bl/6J and Balb/c mice, and transgenic C57Bl/6J *nu/nu* mice (devoid of mature T cells) were supplied by the Animal Breeding Center of The Weizmann Institute of Science. Animals were handled according to the regulations formulated by IACUC (Institutional Animal Care and Use Committee).

2.2. Antigens

MBP from guinea pig spinal cord and ovalbumin (OVA) were purchased from Sigma (St. Louis, MO). MBP peptides MBP 51–70 (APKRGCGKDSHTRTTHYG) and MBP 87–99 (VHFFKNIVTPRTP) were synthesized using 9-fluorenylmethoxycarbonyl technique with an automatic multiple peptide synthesizer (AMS422; ABIMED, Langenfeld, Germany) at the Weizmann Institute of Science. The encephalitogenic peptide myelin oligodendrocyte glycoprotein (MOG) 39–48 was synthesized at The Weizmann Institute of Science.

2.3. Antibodies

Mouse anti-rat CD4 antibodies conjugated to phycoerythrin and mouse anti-rat CD8 antibodies conjugated to fluorescein isothiocyanate were purchased from Serotec (Oxford, UK).

2.4. Optic nerve crush in rats and mice

The optic nerve was crushed as previously described in detail (Yoles and Schwartz, 1998). Using a binocular operating microscope, we anesthetized the animals and exposed their right optic nerves. In rats, we used calibrated cross-action forceps to inflict a moderate or severe crush injury on the optic nerve, 1–2 mm from the eye. The severity of the injury determines the number of directly injured neurons. To assess neuroprotection, we inflicted a moderate crush injury on the optic nerve in Lewis rats (severe crush in this strain leaves almost no viable retinal ganglion cells (RGCs) because of poor endogenous neuroprotection) and a severe crush in SPD rats. To assess systemic and local inflammatory effects, we inflicted a severe crush in both strains. In mice, we inflicted a severe crush injury on the intraorbital portion of one optic nerve, leaving the contralateral nerve undisturbed.

2.5. Measurement of secondary neuronal degeneration in rats

Secondary degeneration of optic nerve axons was assessed by retrograde labeling of RGCs. This was done by the application, 2 weeks after crush injury, of the fluorescent lipophilic dye 4-(4-(didecylamino)styryl)-*N*-methylpyridinium iodide (4-Di-10-Asp) (Molecular Probes Europe, Leiden, The Netherlands) distally to the site of lesion, as previously described (Yoles and Schwartz, 1998).

2.6. Retrograde labeling of retinal ganglion cells in mice

This procedure was performed as previously described (Schori et al., 2001). The neurotracer dye FluoroGold (5% solution in saline; Fluorochrome, Denver, CO) was injected into the anesthetized mouse (1 μl at a rate of 0.5 μl/min in each hemisphere) using a Hamilton syringe, at a depth of 2 mm from the exposed brain surface, 2.92 mm posterior to the bregma and 0.5 mm lateral to the midline. One week after crush injury, the mice were killed and their retinas were detached and prepared as flattened whole mounts in 4% paraformaldehyde solution. Labeled cells from four to six selected fields of identical size (0.7 mm^2) were counted.

2.7. Enzyme-linked immunosorbent assay

Anti-MBP T cells were grown for 1 week in a propagation medium, then washed with phosphate-buffered saline (PBS) and resuspended in stimulation medium. The T cells (0.5×10^6 cells/ml) were incubated, in the presence of irradiated thymocytes (10^7 cells/ml), with ConA (1.25 μg/ml), or with MBP antigen (10 μg/ml), or with no antigen, in stimulation medium at 37 °C, 98% relative humidity and 10% CO_2. After 48 h, the cells were centrifuged and their supernatants were collected and sampled according to the standard sandwich ELISA protocol for IFN-γ and IL-10 (R&D Systems, Minneapolis, MN). The plates were developed using a 3,3′,5,5′-tetramethyl-benzidine liquid substrate system (Sigma). The reaction was stopped by addition of 1 M H_3PO_4, and the optical density was determined at 450 nm.

2.8. T cell lines

T cell lines were generated from draining lymph node cells obtained from Lewis rats immunized with the relevant antigens, as previously described (Moalem et al., 1999).

2.9. FACS analysis of $CD4^+$ and $CD8^+$ T cells

Cells were immunostained according to the manufacturer's instructions and were resuspended in 0.4 ml of 1% paraformaldehyde and analyzed by FACSsort (Becton-Dickinson), with 10,000 events scored. In single-color analysis, positive cells were defined as cells with higher immunofluorescence values, on a logarithmic scale, than those of control cells incubated with isotype antibodies as a control. The cells were scored from a region defined according to physical parameters that indicate the size (forward scatter) and granularity (side scatter) of lymphocytes, and were gated for staining with anti-CD4 and anti-CD8 antibodies.

2.10. Preparation of splenocytes

Donor splenocytes from rats (aged up to 10 weeks) were obtained by rupturing the spleen and following conventional procedures. The splenocytes were washed with double-distilled water to eliminate red blood cells. Cells were run on a gradient of LSM® (Cappel, Aurora, OH) according to the manufacturer's instructions. Cells from the interphase were washed with PBS and counted.

2.11. Enrichment of mouse CD-positive T cells from splenocytes

$CD4^+$ T cells were purified using the StemSep™ method for separation of murine cells (StemCell Technologies, Vancouver, BC, Canada). Splenocytes were isolated as described above and incubated with monoclonal antibodies CD11b (MAC-1), CD45R (B220), and CD8, myeloid differentiation antigen (Gr-1), and erythroid cells (TER119). This "depletion cocktail" is tailored for enrichment of $CD4^+$ T cells (we achieved a purity of ~80%). Cells were separated using the standard StemCell™ protocol, using a magnetic

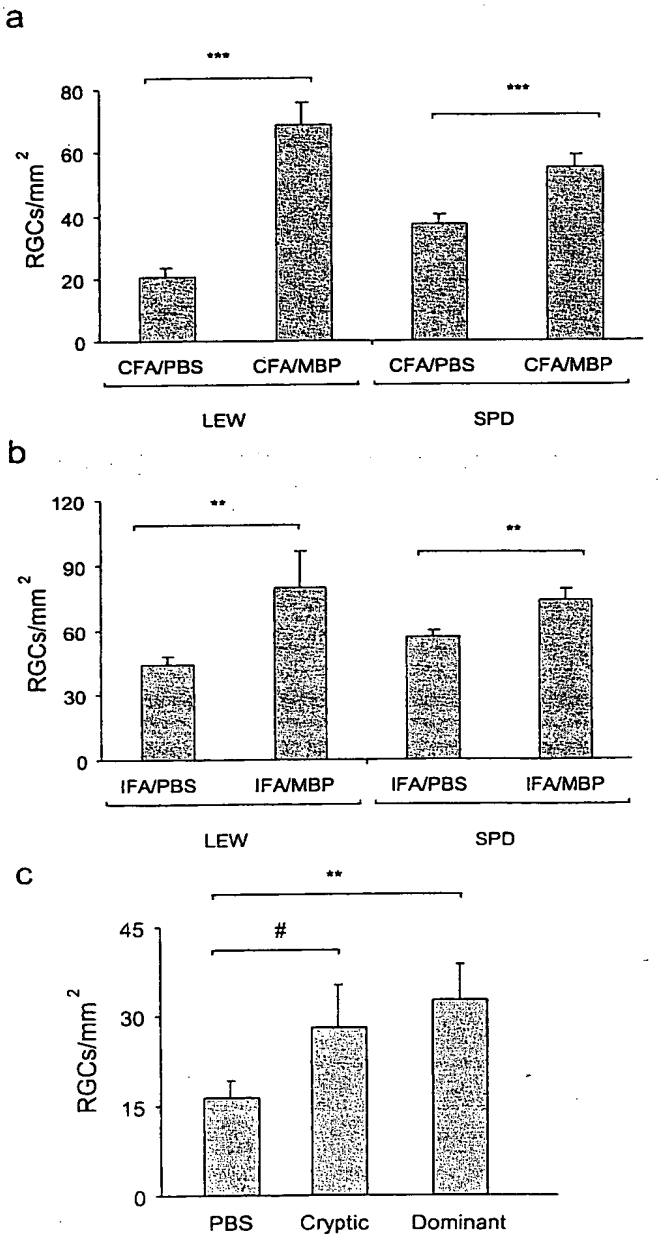


Fig. 1. Active immunization with MBP or MBP-derived peptides has a neuroprotective effect in both susceptible and resistant rat strains: susceptible Lewis and resistant SPD rats were immunized with 100 μg of MBP or with PBS emulsified in (a) complete Freund's adjuvant (CFA) or (b) incomplete Freund's adjuvant (IFA), 1 week before being subjected unilaterally to severe (a) or moderate (b) optic nerve crush injury (n=10–12 rats in each group). (c) Lewis rats were immunized with 100 μg of a cryptic (51–70) or a dominant (87–99) epitope of MBP, or with PBS emulsified in CFA, 1 week before being subjected unilaterally to severe optic nerve crush (n=10–12 rats in each group). To assess secondary degeneration, 2 weeks after injury, we applied the neurotracer dye 4-Di-10-Asp distally to the injury site, and 5 days later the rats were killed and their retinas were excised and flat-mounted. Labeled RGCs (representing surviving fibers), from four fields located at approximately the same distance from the optic disk in each retina, were counted under the fluorescence microscope. The neuroprotective effect (assessed by the number of neurons that survived the injury) of prior immunization with MBP emulsified in CFA (a) or IFA (b) was significantly greater than that of injection with PBS in the susceptible Lewis rats (P<0.001 or P<0.01, respectively, Student's t-test) as well as in the resistant SPD rats (P<0.001; P<0.01 respectively). The neuroprotective effect of prior immunization with the dominant epitope emulsified in CFA (c) was significantly greater than that of injection with PBS (P<0.01; Student's t-test) whereas immunization with the cryptic epitope was significant relative to PBS injection only when tested by a one-tailed Student's t-test (P=0.082 and P=0.041 for two-tailed and one-tailed Student's t-test, respectively).

cell depletion technique. Recovered cells were not labeled with antibody.

2.12. In vitro proliferative response of splenocytes

Splenocytes prepared from treated rats (quadruplicate samples for each rat) were assayed in 96-well plates. Each well contained 5×10^5 cells and antigens, as described in Results. When T cells were to be used as antigens, they were lethally irradiated (2000 rad) before use. The cells were cultured in 0.1 ml of proliferation medium for 48 h at 37 °C in humidified air with 7.5% CO_2. Cultures were pulsed with [^{3}H]-thymidine for the last 18 h and then harvested by a multi-harvester on fiberglass filters. Thymidine incorporation was measured in a liquid scintillation counter.

2.13. Clinical score for experimental autoimmune disease

Symptoms of EAE were evaluated and graded on a 5-point scale: 0.5, loss of tail tonus; 1, tail paralysis; 2, gait disturbance; 3, hind limb paralysis; 4, tetraparesis; 5, death.

3. Results

3.1. Active immunization with myelin basic protein emulsified in incomplete or complete Freund's adjuvant protects neurons from secondary degeneration

Previous studies in our laboratory have shown that autoimmune T cells reactive to MBP confer neuroprotection when injected systemically into recipients with a CNS injury (optic nerve crush or spinal cord contusion), despite the fact that the treated animals also develop the transient autoimmune disease EAE. Here we show that neuroprotection can also be induced by active immunization of EAE-susceptible (Lewis) rats with MBP emulsified in complete Freund's adjuvant (CFA). Similar active immunization of the EAE-resistant SPD rats conferred neuroprotection (Fig. 1a). To verify that it is possible to obtain neuroprotection without inducing EAE in Lewis rats, we immunized rats of both strains with MBP emulsified in incomplete Freud's adjuvant (IFA). In both cases, a neuroprotective effect, without EAE development, was obtained (Fig. 1b).

We further examined whether treatment efficacy would be affected by the nature of the myelin-derived peptide. A neuroprotective autoimmune response was demonstrated in Lewis rats immunized with the cryptic epitope (51–70) of MBP, but the response was not as strong as that in rats immunized with the MBP dominant epitope (87–99). The latter group of rats, despite developing severe autoimmune disease, derived significant benefit from the vaccination (Fig. 1c).

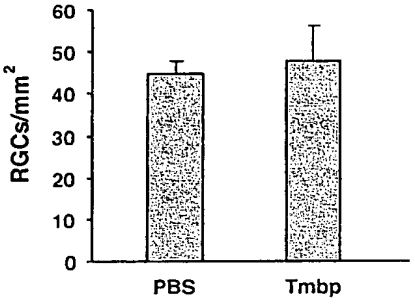
3.2. Autoimmune Th1 cells confer neuroprotection on damaged neurons only when they act in conjunction with additional CD4-positive T cells

We first examined whether the cells that are neuroprotective in EAE-susceptible recipients are the injected anti-MBP T cells themselves or endogenous cells evoked in response to the injection.

Normal adult Lewis rats (an EAE-susceptible strain) and adult Lewis rats in which the thymus had been excised at birth were subjected to unilateral moderate optic nerve crush, followed immediately by passive transfer of autoimmune anti-MBP helper T cells (mostly Th1 cells), a population previously shown to be encephalitogenic (Moalem et al., 1999). Unlike the normal rats, the neonatally thymectomized rats received no benefit from the transferred of the anti-MBP helper T cells: the numbers of their RGCs per square millimeter (mean±SEM) were 48±8 after the T cell transfer and 45±3 without the transferred T cells (Fig. 2a). They did, however, develop EAE (Fig. 2b), as the transferred line was encephalitogenic, CD4$^+$, reactive to MBP, and mostly of the Th1 phenotype, especially upon activation (Fig. 2c–e). When we transferred the MBP-reactive T cells into thymectomized Lewis rats along with an enriched population of CD4$^+$ T cells (90–95% pure; isolated from the spleens of naïve Lewis rats; Fig. 2f) a significant neuroprotection following optic nerve crush in these rats was observed (Fig. 2g). These results thus suggest that a CD4 population of the recipient is involved in the process of the immune neuroprotection in addition to the transferred Th1 cells.

The encephalitogenic T cells used in our experiments were not cloned, but were derived from a rat primary T cell line which expresses a cytokine profile reminiscent of Th1/Th0 (Moalem et al., 2000a) (Fig. 2). To verify our assumption that the same T cell population is active in both autoimmune disease induction and immune neuroprotection, we conducted a similar experiment in mice, using the EAE-susceptible C57Bl/6J strain and cloned Th1 cells specifically directed to the dominant epitope (35–55) of the myelin-associated antigen MOG (Fig. 3a). An examination of the cytokine content of the Th1 clones showed that these T cells produce large quantities of IFN-γ but no detectable levels of IL-4 (Mizrahi et al., manuscript in preparation). Passive transfer of these homologous anti-MOG Th1 cells into wild-type C57Bl/6J mice after optic nerve injury was beneficial, resulting in the survival of significantly more RGCs than in untreated matched controls (806±48 compared to 599±87; $p<0.05$; Fig. 3b). No such beneficial effect was obtained when the same cells were injected into nude (*nu/nu*) C57Bl/6J mice lacking mature T cells (398±55 compared to 419±55 in the controls). These results provide further evidence that the same population of T cells participates in both the beneficial (neuroprotective) and the destructive (disease-inducing) autoimmune response. They also lend further support to our contention

a



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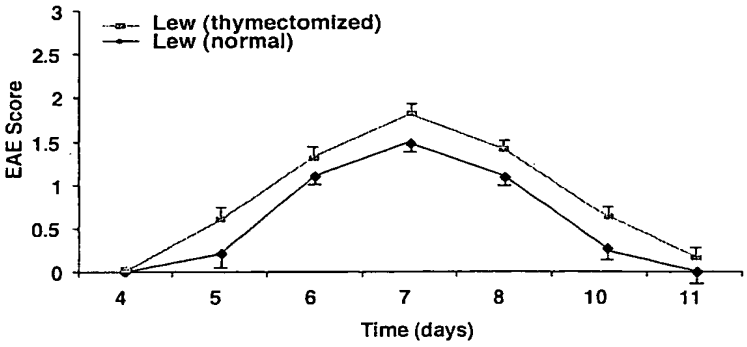

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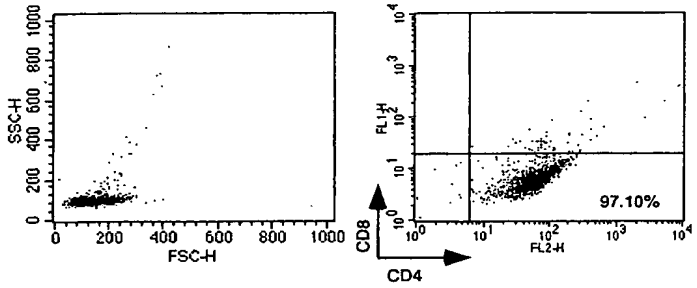


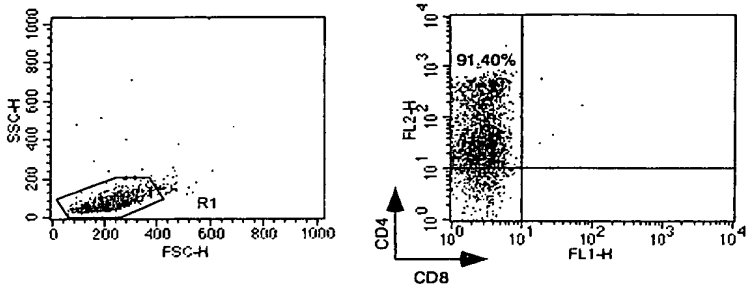
d

	T cells only	Stimulation with MBP	Stimulation with ConA
3H incorporation (CPM±SEM)	323 ± 39	5636 ± 420	24319 ± 1121

e

	Resting State	Stimulation with MBP	Stimulation with ConA
IFN-γ (pgr/ml)	725	15692	22758
IL-10 (pgr/ml)	41	1941	3565

f



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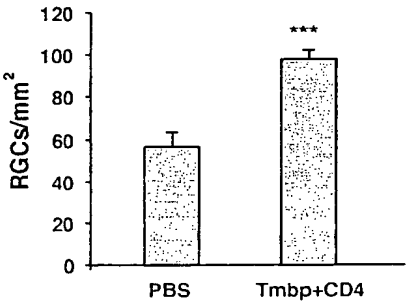


Fig. 2.

a

	T cells only	Stimulation with Mog	Stimulation with ConA
3H incorporation (CPM±SEM)	1198±119	11625±1130	9414±926

b

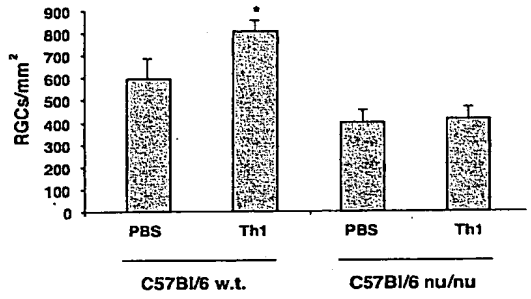
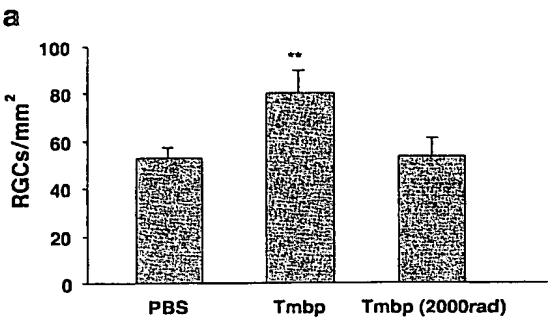


Fig. 3. The transferred autoimmune T cells responsible for evoking neuroprotection are Th1 cells: (a) Immediately after optic nerve crush injury, adult C57Bl/6J wild-type mice and C57Bl/6J *nu/nu* mice (devoid of T cells) were injected with a Th1 clone directed against a MOG-derived peptide. Injection of T cells into the wild-type mice resulted in increased neuronal survival (n=5 in each group; P<0.05; Student's t-test) relative to that in control mice injected with PBS only. Similar injection of Th1 cells into the *nu/nu* mice had no effect. (b) Thymidine incorporation assay of the T cells shows a strong antigenic specificity of this clone, compared to non-antigen mitogenic activation.

a



b

T cells injected/ Stimulatory Ag	Tmbp (CPM±SEM)	Tmbp (2000rad) (CPM±SEM)
Tmbp	6100±900	6600±1200
Ova	3719±432	3605±385
Con A	30656±2166	29238±1773

Fig. 4. T cells reactive to myelin basic protein, if not viable, lose their neuroprotective effect; T cell vaccination with lethally irradiated cells is not sufficient to induce neuroprotection: (a) Injection of viable autologous anti-MBP T cells into Lewis rats increased neuronal survival after optic nerve injury (Student's t-test; P<0.01 compared with PBS injection), whereas injection of lethally irradiated anti-MBP T cells had no such effect (n=8–10 in each group, Student's t-test; p>0.5). (b) Injection of irradiated and of viable T cell lines induced a similar T cell response, measured by a proliferation assay specific to the injected T cells (anti-idiotypic response) (n=8–10 for each T cell treatment).

that protective autoimmunity requires the participation of myelin-specific Th1 cells. It appears, however, that expression of the beneficial effect of the injected Th1 cells in addition to or instead of destruction, requires an additional mechanism, supplied by a T cell population that is missing in the nude mice.

3.3. Passive transfer of non-viable T cells fails to promote neuronal survival

The finding that passively transferred myelin-specific autoimmune T cells are beneficial in rats and mice only when $CD4^+$ T cells are present in the recipients prompted us to examine whether the transferred cells are themselves the active players inducing protection, or are needed to evoke a T cell-dependent protective mechanism in the recipient. To address this question, we injected the optic nerve-injured Lewis rats with encephalitogenic autoimmune T cells that had been lethally irradiated. Matched injured Lewis rats injected with non-irradiated encephalitogenic T cells served as a positive control. Injection of the irradiated cells into Lewis rats with an intact thymus failed to elicit a neuroprotective response (mean numbers of RGCs per square millimeter were 52±4 without the injected T cells and 53±8 after T cell transfer; Fig. 4a), in spite of the fact that this procedure evoke a proliferative response directed to the injected inactivated T cells, similar to that evoked by injection of viable T cells (Fig. 4b) (Borghans et al., 1998).

4. Discussion

In this study, we showed that Th1 cells are needed for expression of the beneficial effect of autoimmunity after axonal injury in the CNS. We further showed that active immunization with an encephalitogenic myelin-related self-

Fig. 2. The transferred autoimmune T cells reactive to myelin proteins are necessary but not sufficient for immune neuroprotection: the recipient $CD4^+$ T cells are also required: (a) Anti-MBP T cells (mostly Th1 cells) injected immediately after optic nerve crush injury in adult Lewis rats, though strongly neuroprotective in normal rats, had no effect if the rats had been thymectomized at birth and therefore were devoid of endogenous T cells (n=8–10 in each group; Student's t-test; P>0.5). (b) The injected anti-MBP T cells were examined for expression of CD4 and CD8 surface markers by FACS (c) examined for expression of cytokines (IFN-γ and IL-10), and (d) assayed for thymidine incorporation to ensure antigen-specific activity. (e) The thymectomized recipients developed a monophasic EAE, similar to that seen in normal rats upon injection of the anti-MBP T cells. (f) Co-transfer of autoreactive T cells and naïve $CD4^+$ T cells restored the neuroprotective effect (n=6–8 in each group; P<0.001; Student's t-test). $CD4^+$ T cells were purified as described in Materials and methods. Their purity was found to range from 90% to 95% (a representative level of purification is presented (g)).

antigen has a beneficial effect on neuronal survival in rats after CNS injury (optic nerve crush). It appears that the requirements for neuroprotection and for induction of an autoimmune disease (EAE) are not the same, even though the activity of myelin-specific Th1 cells is common to both. Neuroprotection could be achieved under conditions (immunization with IFA) that did not allow EAE to develop, but at the same time a strong autoreactive response (obtained with a dominant epitope but not with a cryptic epitope) was needed for neuroprotection. For autoimmune disease induction the transfer of effector Th1 cells alone is sufficient, whereas for neuroprotection both the effector Th1 cells and another population of T cells, namely $CD4^+$ cells that are endogenous to the recipient, are required.

Previous studies in our laboratory, showing that autoimmune T cells reactive to MBP confer neuroprotection on the damaged optic nerve, raised a fundamental question: is an active autoimmune activity required for neuroprotection or do the injected autoimmune T cells increase the regulatory network represented in part by anti-idiotypic T cell activity? The results of the present study show that active immunization of EAE-susceptible rats with MBP, emulsified in either CFA or IFA, has a strong neuroprotective effect. Since an autoimmune disease is not induced with IFA as emulsifier, it follows that autoimmune disease development is not a prerequisite for manifestation of protective autoimmunity. Interestingly, however, rats immunized with a dominant epitope of MBP showed significantly better neuronal survival than rats immunized with a cryptic MBP epitope, suggesting that neuroprotection probably requires the presence of a critical number of potent autoreactive T cells. These findings, together with others (Butovsky et al., 2001; Hammarberg et al., 2000a,b), raised questions about the relationship between the T cells that confer neuroprotection and those that cause a disease. Are they the same or different, and does either of these T cell populations need the participation of other cells for its operation?

An earlier study from our laboratory showed that after CNS injury in an EAE-susceptible (Lewis) strain, passive transfer of encephalitogenic T cells specific to myelin-associated antigens, in spite of inducing EAE, protects the damaged nerve from secondary neuronal degeneration (Hauben et al., 2000a; Moalem et al., 1999). In the present work the same cells, when injected into Lewis recipients devoid of mature T cells (due to neonatal thymectomy), were found to induce EAE, but without any neuroprotective benefit to the injured neural tissue. When these autoimmune T cells were co-injected with homologous purified $CD4^+$ T cells into the thymectomized Lewis recipients, their beneficial effect was restored. No neuroprotection was observed, however, if the transferred cells were lethally irradiated, although the transferred cells were still capable of inducing a proliferative T cell response similar to that obtained with live transferred T cells. We conclude that passive transfer of live autoimmune T cells can beneficially affect the survival of injured neural tissue provided that an additional T cell population ($CD4^+$), endogenous to the recipient, is also present. The nature of this population and their role in protective autoimmunity is currently under investigation.

The results of this study further show that the beneficial outcome of an autoimmune T cell response is mediated by Th1 cells. Injection of Th2 cells does not induce neuroprotection (Mizrahi et al., manuscript in preparation). It should be noted that immunization in the resistant strain of SPD rats causes the spontaneous autoimmune protective response to be boosted, whereas in the susceptible Lewis rats, in which such a response is not spontaneously manifested, such immunization causes its induction. The Th1 response is significantly stronger when the adjuvant used for immunization is CFA rather than IFA (Lenz et al., 1999; Shibaki and Katz, 2002; Zhang et al., 1999). This might explain why immunization with CFA has a much more potent neuroprotective effect than immunization with IFA. Immunization with IFA is known to evoke the Th2 phenotype. At an early stage after the immunization, however, it evokes a short-lived Th1 phenotype (Shibaki and Katz, 2002; Zhang et al., 1999), which is apparently sufficient to accommodate the neuroprotective activity of Th1 cells within the therapeutic window of an acute insult. By the time the response shifts to evoking Th2, the relevant therapeutic window would in any case no longer be open. This might explain the efficacy of immunization with IFA.

We suggest that the activity of the Th1 cells in neural protection (i.e., in their response to self-antigens) does not differ from the activity of helper Th1 cells in their response to nonself antigens, i.e., providing well-controlled assistance to macrophages or other phagocytic or antigen-presenting cells in their activity of removing a perceived threat to the tissue by amplifying the innate response (Shaked et al., unpublished observations).

According to this view, the difference between beneficial autoimmunity (neuroprotection) and potentially destructive autoimmunity (autoimmune disease) derives not from the nature of the autoimmune T cells but from their regulation, which presumably affects such parameters as the time of onset, the strength, and the duration of the autoimmune response manifested at the site of a CNS insult. Therefore, contrary to the prevailing perception of autoimmunity as an accident of nature with consequences that are always harmful, we suggest that autoimmunity should instead be viewed as a desirable and beneficial response, though in need of proper regulation in order to fulfil its protective potential (Schwartz and Kipnis, 2001).

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